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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (51) International Patent Classification ⁶ : A61K 7/42, 7/06, 7/48 | | A1 | (11) International Publication Number: WO 99/37279 (43) International Publication Date: 29 July 1999 (29.07.99) |
| (21) International Application Number: PCT/EP98/07218 | | | (72) Inventors: RAGHUPATHI, Subramanian; Hindustan Lever Ltd., Research Centre, Chakala, Andheri (East), Mumbai 400 099 (IN). RAMAIAH, Abduri; Dept. of Biochemistry, PVNR Medical College, Himalayan Institute of Medical Science, Jolly Grant, Dehradun, UP 248 140 (IN). RAMAN, Govindarajan; Hindustan Lever Ltd., Research Centre, 64 Main Road, Whitefield P.O., Bangalore 560 066 (IN). WAGH, Sushama, Shripad; Hindustan Lever Ltd., Research Centre, 64 Main Road, Whitefield P.O., Bangalore 560 066 (IN). |
| (22) International Filing Date: 9 November 1998 (09.11.98) | | | (74) Agent: MOLE, Peter, Geoffrey; Unilever PLC, Patent Dept., Colworth House, Sharnbrook, Bedford MK44 1LQ (GB). |
| (30) Priority Data: 9801191.9 20 January 1998 (20.01.98) GB | | | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). |
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(54) Title: SKIN AND HAIR DARKENING COMPOSITION

(57) Abstract

A cosmetic skin/hair darkening composition for topical application to skin and/or hair is provided that comprises from 0.1 to 10 % by weight of a peptide having an isoelectric point ranging from 6 to 11.

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SKIN AND HAIR DARKENING COMPOSITION

The present invention relates to a cosmetic composition for darkening the skin and/or hair. The invention also relates 5 to a method of topically applying to the skin and/or hair a skin/hair darkening composition according to the invention.

Skin tanning by UV exposure is a well known phenomenon. 10 However, it is also well known from the literature that such exposure to UV radiation results in accelerated aging of skin and increased incidence of skin cancer. Accordingly, alternative modes of skin tanning have evolved. It is presently known in the art to use dihydroxy acetone (DHA) as a non-UV induced tanning aid. However, undesirably, the use 15 of dihydroxy acetone for skin tanning purposes produces a rather unnatural looking sun tan. Further, the artificial tan produced by DHA does not protect against UV irradiation as would a natural tan.

20 Melanin is the black pigment of hair and skin and is synthesized from the amino acid tyrosine by melanosomes. Melanosomes are organelles found in melanocytes, a cell type present at dermis-epidermis junction. Tyrosine is acted upon by an enzyme, tyrosinase, which is the key step in 25 melanogenesis.

In the melanosomes the melanin is synthesized from monomers and is transferred to the neighbouring cells called keratinocytes. The keratinocytes divide and differentiate 30 and thus transport the melanosome to the surface of the skin. The intensity of the skin colour is directly related to the

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number, the size, melanin content, the rate of formation and migration/transfer of melanosomes to keratinocytes.

Several specific sequences of polyaminoacids and peptide 5 residues are known to inhibit melanin pigmentation and have a whitening effect on the skin (JP 6345797; JP 6321757; JP 6321755; JP5170636; US 5,126,327).

The peptides described in the prior art comprise a high 10 proportion of basic and hydrophobic amino acids and have isoelectric point (pI) values greater than 5.5. These are mainly used for lightening the hyperpigmented areas associated with abnormal skin conditions.

15 The applicants in their co-pending British patent application 9719195.1, disclose a cosmetic composition for lightening the skin comprising from 0.1 to 10% by weight of a peptide with an isoelectric point of between 2 and 5.5. Isoelectric point (pI) is defined as the pH at which net charge on a molecule 20 is zero. Peptides having large number of acidic amino acids like glutamic acid, aspartic acid etc. have a low pI and those having basic amino acids like lysine, arginine, histidine have a high pI.

25 The Applicants have found that a composition comprising peptide sequences having a isoelectric point (pI) of between 6 and 11 is capable of darkening the skin/hair.

Accordingly, the present invention relates to a cosmetic 30 skin/hair darkening composition comprising from 0.1% to 10%

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by weight of a peptide with an isoelectric point (pI) ranging from 6.0 to 11.

5 The skin/hair darkening effected by the composition of the invention is reversible and without any side effects. The composition according to the invention is active during both day and night.

10 The peptide is a sequence of amino acids and is of molecular weight ranging from 200 to 20,000 daltons (Da) with a pI ranging from 6.0 to 11.0. The peptide is also optionally linked to a hydrophobic amino acid or a targeting molecule or vehicle.

15 The amino acid residues forming the peptide sequence can be naturally occurring or synthetic, dextro or levo form, and includes any derivative thereof. The peptide sequence must comprise a proportion of the basic amino acids such that the resulting peptide is basic in nature. The peptide sequence 20 may be straight chain or cyclic.

The molecular weight of the peptide sequence ranges from 200 to 20,000 Da and preferably from 200 to 2000 Da.

25 The pI of the peptide sequence ranges from 6.0 to 11.0.

The hydrophobic amino acid can be chosen from any one of alanine, isoleucine, leucine, methionine, phenyl alanine, proline, tryptophan or valine and is preferably tryptophan.

30 The targeting molecule is preferable a peptide and most preferably a hexapeptide preferably having the primary

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sequence asparagine-glutamine-proline-leucine-leucine-threonine, and is located within 27 amino acid residue from the carboxy terminal of the active peptide. Targeting vehicles such as micelles and/or reverse micelles, may also 5 be used.

According to a preferred aspect of the invention there is provided a cosmetic skin/hair darkening composition comprising from 0.5 to 5.0% by weight of the peptide.

10

The invention further relates to a cosmetic method of darkening skin/hair comprising topically applying to the skin and/or hair a composition according to the invention.

15 The composition may also comprise a skin tanning agent. This tanning agent may be chosen from any known agent for this purpose such as dihydroxy acetone, theophyllin, copper gluconate, natural actives obtained from *Pterocarpus santalinus*, and any other known skin tanning agents..

20 The composition according to the invention may also comprise a cosmetically compatible carrier. It may also comprise preservatives, emulsifiers, thickeners, perfume, colour, skin benefit materials such as moisturisers, emollients and antiageing compounds.

25

The vehicle which forms part of the cosmetic composition is one or more substances which are compatible with the polyamino acid sequence and which are also cosmetically acceptable in that they will not harm the skin/hair. The 30 vehicles that can be used in the compositions according to the invention can include powder absorbents, binders and

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carriers, and liquids such as emollients, propellants, solvents, humectants and thickeners. Also simple vehicles such as alcohol, PEG, propylene glycol may also be used.

5 Examples of moisturisers and humectants include polyols, glycerol, cetyl alcohol, carbopol 934, ethoxylated castor oil, paraffin oils, lanolin and its derivatives. Silicone compounds such as silicone surfactants like DC3225C (Dow Corning) and/or silicone emollients, silicone oil (DC-200 Ex-
10 Dow Corning) may also be used.

The compositions according to the invention may be prepared for topical application to the skin/hair in the form of simple solutions or conventional leave-on or wash-off
15 products such as lotions, creams, ointments, shampoos and/or aerosol products.

All percentages referred to herein and in the appended claims are by weight of the composition unless otherwise indicated.

20 The invention will now be illustrated by way of Examples. The Examples are for illustration only and do not in any way restrict the scope of the invention.

25 **Example 1**

In vitro demonstration of enhancement of melanin formation

30 The influence of a peptide sequence with pI 11.0 on the formation of melanin at pH 5 in an *in vitro* system, comparable to the pH of the melanosomal system, was analysed.

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The assay conditions for the formation of melanin under *in vitro* conditions are as follows.

Assay method

5

The control assay mixture contained 5 μ moles of DL-DOPA (Dihydroxy phenyl alanine), 20nmoles lysozyme and 3.2 units of tyrosinase in acetate buffer pH 5.0 in a test tube. A unit is defined as the amount of tyrosinase needed to convert 10 1 nmol DOPA in one minute. In the experimental set 11 nmoles of polylysine, a polyamino acid sequence with pI 11.0, was used in addition to the other ingredients as defined in the control. The melanin formed was washed with the acetate buffer, suspended in 1N sodium hydroxide and dissolved by 15 heating the sample at 60°C for 5 minutes. The absorbance was measured at 400 nm.

Table 1

| Sample | Melanin formed A 400 |
|---------------------------|----------------------|
| Control | 0.120 |
| In presence of polylysine | 0.168 |

20 The above results show that in the presence of polylysine sequence the melanin production is significantly enhanced.

The invention will now be illustrated by reference to the following example of a cosmetic cream.

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| Composition %Wt. | Comparative Example | EXAMPLE 2 |
|-------------------------|---------------------|-----------|
| Stearic acid | 2.5 | 2.5 |
| Cetyl alcohol | 0.2 | 0.2 |
| Silicone oil | 0.5 | 0.5 |
| Isopropyl myristate | 2.0 | 2.0 |
| Glyceryl monostearate | 1.5 | 1.5 |
| Methyl/Propyl paraben | 0.3 | 0.3 |
| Glycerine | 1.0 | 1.0 |
| EDTA disodium salt | 0.04 | 0.04 |
| Light paraffin oil | 1.5 | 1.5 |
| Triethanolamine | 0.5 | 0.5 |
| Carbopol 941 | 0.5 | 0.5 |
| Dihydroxy acetone | 2.0 | 2.0 |
| Perfume | 0.3 | 0.3 |
| Polyamino acid (pI6-11) | - | 5.0 |
| Water | to 100 | to 100 |

Application of the cosmetic cream described in the Comparative Example and Example 2 will show that the product described in Example 2 will be significantly superior in 5 darkening the skin to that of the Comparative Example.

It is thus possible by way of the present invention to provide for a skin/hair darkening composition which is reversible and without any side effects. The composition is 10 active both during day and night.

The figures in the table represent percentages of the composition by weight.

Example 3In vitro demonstration of enhancement of melanin formation

5 The influence of the polyamino acid sequence with polyglutamate pI 2.5, polyarginine (pI 10.9) or polylysine (pI 11.0) on the formation of melanin at pH 5 in an *in vitro* system, comparable to the pH of the melanosomal system, was analysed. The assay conditions for the formation of melanin 10 under *in vitro* conditions are as follows.

Assay method:

The control assay mixture contained 5 mmoles of DL-DOPA 15 (Dihydroxy phenyl alanine), lysozyme 20 nmoles and 0.45mg of tyrosinase in acetate buffer pH 5.0 in a test tube. In the experimental set 18 nmoles of the polyglutamate, a polyamino acid sequence with pI 2.5 or polyarginine pI 10.9 or polylysine pI 11.0 was used in addition to the other 20 ingredients as defined in the control. The melanin formed was washed with the buffer, suspended in 1 N sodium hydroxide and dissolved by heating the sample at 60°C for 5 minutes. The absorbance was measured at 400 nm.

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Table 2

| Sample | Melanin formed A 400 |
|-------------------------------------|----------------------|
| Control | 0.120 |
| In presence of polyglutamate pI 3-4 | 0.048 |
| In presence of polylysine pI 11.0 | 0.168 |
| In presence of polyarginine pI 10.9 | 0.182 |

5 The above results show that in the presence of polyamino acid sequence with alkaline pI or pI > 5.0 the melanin production is significantly enhanced whereas in the presence of polyamino acid sequence with pI in the acidic range we do not get a similar enhancement in melanin production.

10

Example 4

In vivo demonstration of enhancement of melanin formation

15 Twelve female volunteers having even-toned skin and with no scars/visible hair on the forearms were chosen. On the volar side of the forearm 1 square cm. sites were marked using a template. A mixture of peptides of a molecular weight ranging from 14 K daltons, having a pI 11.2 at a

20 concentration of 2% in a suitable vehicle was used. The above

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solution contained 0.3 μ g protein/ μ l and 5ml of this was applied for ten days. The untreated and placebo (Vehicle) served as controls. The sites were graded by an expert, who was blinded to the treatment assignments, on zero day and on 5 11th day. The data is presented in table 3 shows that even under *in vivo* conditions peptides with a pI > 5.0 darken the skin significantly as compared to the two controls, namely the untreated and vehicle. The critical difference being 0.12

10

Table 3

| Treatment | Mean change in skin score |
|---------------------|---------------------------|
| Control (untreated) | -0.10 \pm 0.220 |
| Control (vehicle) | 0.050 \pm 0.063 |
| 5% Alkaline peptide | 0.360 \pm 0.074 |

Legends for Expert Evaluation :

| | | | | |
|----|-------------------------|-------|------------------------|-------|
| 15 | SUBSTANTIALLY LIGHTENED | -1.0 | SUBSTANTIALLY DARKENED | +1.0 |
| | DIFINITELY LIGHTENED | -0.75 | DIFINITELY DARKENED | +0.75 |
| | MODERATELY LIGHTENED | -0.5 | MODERATELY DARKENED | +0.5 |
| | SLIGHTLY LIGHTENED | -0.25 | SLIGHTLY DARKENED | +0.25 |
| | NO DIFFERENCE | 0 | | |

20

CLAIMS

1. A cosmetic composition for darkening skin and/or hair comprising from 0.1 to 10%, by weight of a peptide having an isoelectric point ranging from 6 to 11.
5
2. A cosmetic composition according to claim 1 which is topically applied to the skin and/or hair.
- 10 3. A cosmetic composition according to claim 1 or 2 wherein the peptide has a molecular weight of from 200 to 20,000 Da.
- 15 4. A cosmetic composition according to any preceding claim where the peptide is attached to either:
 - a) a hydrophobic amino acid chosen from alanine, isoleucine, leucine, methionine, phenylalanine, valine, proline and tryptophan; or
 - 20 b) a targeting molecule or vehicle.
- 25 5. A cosmetic composition according to claim 4 wherein the hydrophobic amino acid is tryptophan.
6. A cosmetic composition according to claim 4 or 5 wherein the targeting molecule is a peptide.
- 30 7. A cosmetic composition according to claim 4, wherein the targeting molecule is a hexapeptide having the primary sequence (1):

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(1) Asx-Glm-Pro-Leu-Leu-Thr

8. A cosmetic composition according to claim 4, wherein the
5 targeting vehicle is a micelle or reverse micelle.

9. Cosmetic method of darkening skin/hair comprising
topically applying to the skin/hair a composition
according to any preceding claim.

10

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/EP 98/07218

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/42 A61K7/06 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|-----------------------------------------------------------------------------------------------------|-----------------------|
| X | EP 0 293 837 A (SUGIYAMA, KELKICHI) 7 December 1988 see page 2, line 8-11; claims 1,3 ---- | 1-6,9 |
| X | FR 2 608 424 A (CAZACOU, C.) 24 June 1988 see claims 1,3,10,11 ---- | 1-3 |
| X | US 4 866 038 A (HRUBY, V. J. ET AL.) 12 September 1989 see claims 1,12 ---- | 1-3 |
| X | CH 674 310 A (GELMEX FINANCING ESTABLISHMENT) 31 May 1990 see claim 1 ----- | 1-3 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual compilation of the international search

13 April 1999

Date of mailing of the international search report

21/04/1999

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/07218

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The search is incomplete in view of the definition of the peptide (claims 1, 6) by means of physical characteristics only. A search has been performed on the basis of the common inventive concept underlying the present application and the specific compounds mentionned in the examples.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat'l Application No

PCT/EP 98/07218

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
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